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(54) Title: A PHARMACEUTICAL COMPOSITION COMPRISING A P2X₇-RECEPTOR ANTAGONIST AND A TUMOUR NECROSIS FACTOR α

(57) Abstract: The invention provides a pharmaceutical product or kit comprising a first active ingredient which is a P2X₇ receptor antagonist which P2X₇ receptor antagonist is an adamantyl derivative and a second active ingredient which is a tumour necrosis factor α (TNF α) inhibitor, for use in the treatment of inflammatory disorders.

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A pharmaceutical composition comprising a P2X₇-receptor antagonist and a tumour necrosis factor α

The present invention relates to combinations of pharmaceutically active substances for use in the treatment of inflammatory conditions/disorders, especially rheumatoid arthritis.

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Chronic inflammatory disorders such as rheumatoid arthritis are polygenic, highly complex, and involve multiple inflammatory and immune mechanisms. Treatment of these disorders has been largely empirical with a variety of therapeutic agents being used with little understanding of the mechanisms involved. Recent research suggests that two inflammatory mediators, the cytokines IL-1 and TNF α (TNF α), may play key roles in the inflammatory process in rheumatoid arthritis.

10

It would be desirable to develop new pharmaceuticals for use in treating inflammatory conditions/disorders.

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In accordance with the present invention, there is provided a pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a P2X₇ receptor antagonist which P2X₇ receptor antagonist is an adamantyl derivative, and a preparation of a second active ingredient which is a tumour necrosis factor α (TNF α) inhibitor, for simultaneous, sequential or separate use in therapy.

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In another aspect, the invention provides a kit comprising a preparation of a first active ingredient which is a P2X₇ receptor antagonist which P2X₇ receptor antagonist is an adamantyl derivative, a preparation of a second active ingredient which is a tumour necrosis factor α (TNF α) inhibitor, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

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The P2X₇ receptor (previously known as P2Z receptor) is a ligand-gated ion channel that is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes

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(T and B). Activation of the P2X₇ receptor by extracellular nucleotides, in particular adenosine triphosphate, is known to lead, amongst other things, to the release of interleukin-1 β (IL-1 β).

5 An antagonist of the P2X₇ receptor is a compound or other substance that is capable of preventing, whether fully or partially, activation of the P2X₇ receptor.

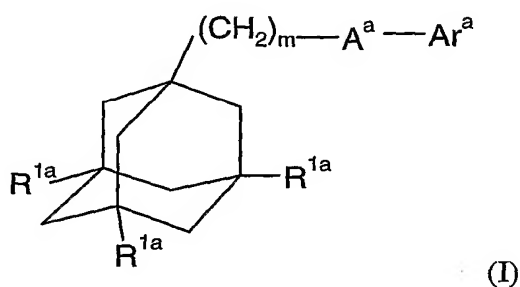
Methods for assaying for P2X₇ receptor antagonism are known in the art, for example from WO 01/42194 which describes an assay based on the observation that when the P2X₇ receptor is activated using a receptor agonist in the presence of ethidium bromide (a
10 fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. Thus, an increase in fluorescence can be used as a measure of P2X₇ receptor activation and therefore to quantify the effect of a compound or substance on the P2X₇ receptor.

15 In WO 01/42194, the assay is carried out by taking a 96-well flat bottomed microtitre plate and filling the wells with 250 μ l of test solution comprising 200 μ l of a suspension of THP-1 cells (2.5×10^6 cells/ml) containing 10^{-4} M ethidium bromide, 25 μ l of a high potassium buffer solution containing 10^{-5} M benzoylbenzoyl adenosine triphosphate (bbATP, a known P2X₇ receptor agonist), and 25 μ l of the high potassium buffer solution
20 containing 3×10^{-5} M test compound. The plate is covered with a plastics sheet and incubated at 37 °C for one hour. The plate is then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X₇ receptor agonist) and pyridoxal 5-phosphate (a
25 P2X₇ receptor antagonist) are used separately in the test as controls. From the readings obtained, a pIC₅₀ figure is calculated for the test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. A pIC₅₀ figure greater than 5.5 is normally indicative of an antagonist.

Examples of P2X₇ receptor antagonists which may be used in accordance with present invention include the compounds described in WO 00/61569, WO 01/42194, WO 01/44170 and WO 03/41707 the entire contents of which are incorporated herein by reference.

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More specifically, in a first embodiment of the present invention the P2X₇ receptor antagonist is a compound of formula

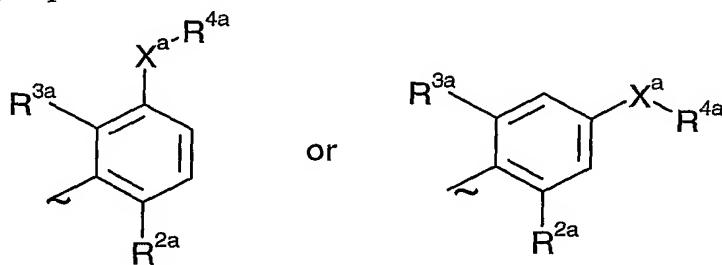


10 wherein m represents 1, 2 or 3;

each R^{1a} independently represents a hydrogen or halogen atom;

A^a represents C(O)NH or NHC(O);

Ar^a represents a group



;

15 X^a represents a bond, an oxygen atom or a group CO, (CH₂)₁₋₆, CH=, (CH₂)₁₋₆O, O(CH₂)₁₋₆, O(CH₂)₂₋₆O, O(CH₂)₂₋₃O(CH₂)₁₋₃, CR'(OH), (CH₂)₁₋₃O(CH₂)₁₋₃, (CH₂)₁₋₃O(CH₂)₂₋₃O, NR^{5a}, (CH₂)₁₋₆NR^{5a}, NR^{5a}(CH₂)₁₋₆, (CH₂)₁₋₃NR^{5a}(CH₂)₁₋₃, O(CH₂)₂₋₆NR^{5a}, O(CH₂)₂₋₃NR^{5a}(CH₂)₁₋₃, (CH₂)₁₋₃NR^{5a}(CH₂)₂₋₃O, NR^{5a}(CH₂)₂₋₆O, NR^{5a}(CH₂)₂₋₃O(CH₂)₁₋₃, CONR^{5a}, NR^{5a}CO, S(O)_n, S(O)_nCH₂, CH₂S(O)_n,
 20 SO₂NR^{5a} or NR^{5a}SO₂;

n is 0, 1 or 2;

R' represents a hydrogen atom or a C₁-C₆ alkyl group;

one of R^{2a} and R^{3a} represents a halogen, cyano, nitro, amino, hydroxyl, or a group selected from (i) C_1 - C_6 alkyl optionally substituted by at least one C_3 - C_6 cycloalkyl, (ii) C_3 - C_8 cycloalkyl, (iii) C_1 - C_6 alkyloxy optionally substituted by at least one C_3 - C_6 cycloalkyl, and (iv) C_3 - C_8 cycloalkyloxy, each of these groups being optionally substituted by one or more fluorine atoms, and the other of R^{2a} and R^{3a} represents a hydrogen or halogen atom;

either R^{4a} represents a 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system containing one or two nitrogen atoms and optionally an oxygen atom, the heterocyclic ring system being optionally substituted by one or more substituents

independently selected from fluorine atoms, hydroxyl, carboxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, $-NR^{6a}R^{7a}$, $-(CH_2)_rNR^{6a}R^{7a}$ and $-CONR^{6a}R^{7a}$,

or R^{4a} represents a 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from $-NR^{6a}R^{7a}$, $-(CH_2)_rNR^{6a}R^{7a}$ and $-CONR^{6a}R^{7a}$, the ring system being optionally further substituted by one or more

substituents independently selected from fluorine atoms, hydroxyl and C_1 - C_6 alkyl; r is 1, 2, 3, 4, 5 or 6;

R^{5a} represents a hydrogen atom or a C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl group;

R^{6a} and R^{7a} each independently represent a hydrogen atom or a C_1 - C_6 alkyl, C_2 - C_6 hydroxyalkyl or C_3 - C_8 cycloalkyl group, or R^{6a} and R^{7a} together with the

nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring;

with the provisos that,

(a) when A^a represents $C(O)NH$ and R^{4a} represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X^a is other than a bond, and

(b) when A^a represents $C(O)NH$ and X^a represents a group $(CH_2)_{1-6}$ or $O(CH_2)_{1-6}$, then R^{4a} does not represent an unsubstituted imidazolyl, unsubstituted morpholinyl, unsubstituted piperidinyl or unsubstituted pyrrolidinyl group, and

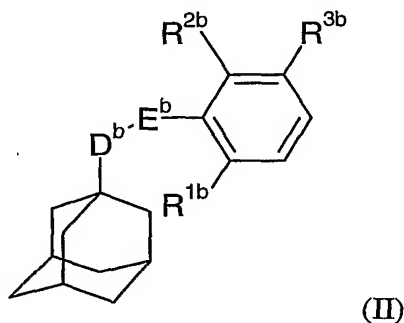
(c) when A^a represents $NHC(O)$ and R^{4a} represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X^a is other than a bond, and

(d) when A^a represents $NHC(O)$ and X^a represents $O(CH_2)_{1-6}$, $NH(CH_2)_{1-6}$ or SCH_2 , then R^{4a} does not represent an unsubstituted 1-piperidinyl or unsubstituted 1-pyrrolidinyl group, and

(e) when A^a represents $NHC(O)$ and X^a represents $O(CH_2)_{2-3}NH(CH_2)_2$, then R^{4a} does not represent an imidazolyl group;
or a pharmaceutically acceptable salt or solvate thereof.

Compounds of formula (I) are described in WO 00/61569.

In a second embodiment of the present invention the $P2X_7$ receptor antagonist is a compound of formula

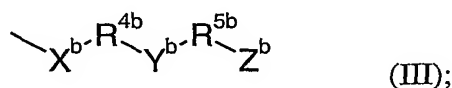


wherein D^b represents CH_2 or CH_2CH_2 ;

E^b represents $C(O)NH$ or $NHC(O)$;

R^{1b} and R^{2b} each independently represent a hydrogen or halogen atom, or an amino, nitro, C_1 - C_6 alkyl or trifluoromethyl group;

R^{3b} represents a group of formula



X^b represents an oxygen or sulphur atom or a group NH , SO or SO_2 ;

Y^b represents an oxygen or sulphur atom or a group NR^{11b} , SO or SO_2 ;

Z^b represents a group -OH, -SH, $-CO_2H$, C_1-C_6 alkoxy, C_1-C_6 alkylthio,

C_1-C_6 -alkylsulphinyl, C_1-C_6 -alkylsulphonyl, $-NR^{6b}R^{7b}$, $-C(O)NR^{8b}R^{9b}$, imidazolyl, 1-methylimidazolyl, $-N(R^{10b})C(O)-C_1-C_6$ alkyl, C_1-C_6 alkylcarbonyloxy,

5 C_1-C_6 alkoxy carbonyloxy, $-OC(O)NR^{12b}R^{13b}$, $-OCH_2OC(O)R^{14b}$, $-OCH_2OC(O)OR^{15b}$ or $-OC(O)OCH_2OR^{16b}$;

R^{4b} represents a C_2-C_6 alkyl group;

R^{5b} represents a C_1-C_6 alkyl group;

R^{6b} , R^{7b} , R^{8b} , R^{9b} , R^{10b} , R^{12b} and R^{13b} each independently represent a hydrogen atom,

10 or a C_1-C_6 alkyl group optionally substituted by at least one hydroxyl group;

R^{11b} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one substituent independently selected from hydroxyl and C_1-C_6 alkoxy; and

R^{14b} , R^{15b} and R^{16b} each independently represent a C_1-C_6 alkyl group;

with the provisos that (i) when E^b represents $NHC(O)$, X^b represents O, S or NH and Y^b

15 represents O, then Z^b represents $-NR^{6b}R^{7b}$ where R^{6b} represents a hydrogen atom and R^{7b} represents either a hydrogen atom or a C_1-C_6 alkyl group substituted by at least one

hydroxyl group, and (ii) when E represents $NHC(O)$, X^b represents O, S or NH, Y^b represents NH and R^{5b} represents CH_2CH_2 , then Z^b is not -OH or imidazolyl;

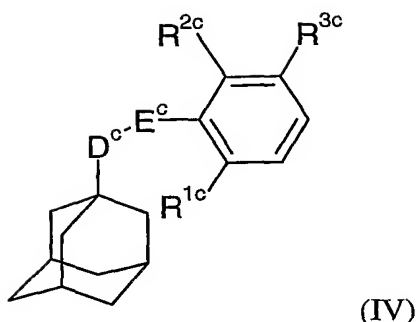
or a pharmaceutically acceptable salt or solvate thereof.

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Compounds of formula (II) are described in WO 01/42194.

In a third embodiment of the present invention the $P2X_7$ receptor antagonist is a compound of formula

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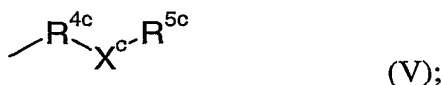
wherein D^c represents CH_2 or CH_2CH_2 ;

E^c represents $C(O)NH$ or $NHC(O)$;

R^{1c} and R^{2c} each independently represent hydrogen, halogen, amino, nitro, C_1 - C_6 alkyl

or trifluoromethyl, but R^{1c} and R^{2c} may not both simultaneously represent hydrogen;

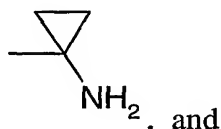
R^{3c} represents a group of formula



R^{4c} represents a C_1 - C_6 alkyl group;

X^c represents an oxygen or sulphur atom or a group NR^{13c} , SO or SO_2 ;

R^{5c} represents hydrogen, or R^{5c} represents C_1 - C_6 alkyl or C_2 - C_6 alkenyl, each of which may be optionally substituted by at least one substituent selected from halogen, hydroxyl, (di)- C_1 - C_6 -alkylamino, $-Y^c-R^{6c}$,



a 5- or 6-membered heteroaromatic ring comprising from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulphur which heteroaromatic ring may itself be optionally substituted by at least one substituent selected from halogen, hydroxyl and C_1 - C_6 alkyl;

Y^c represents an oxygen or sulphur atom or a group NH , SO or SO_2 ;

R^{6c} represents a group $-R^{7c}Z^c$ where R^{7c} represents a C_2 - C_6 alkyl group and Z^c represents an $-OH$, $-CO_2H$, $-NR^{8c}R^{9c}$, $-C(O)NR^{10c}R^{11c}$ or $-N(R^{12c})C(O)-C_1-C_6$ alkyl group, and, in the case where Y^c represents an oxygen or sulphur atom or a group NH , R^{6c} additionally represents hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkylcarbonyl, C_1 - C_6

alkoxycarbonyl, $-\text{C}(\text{O})\text{NR}^{14\text{c}}\text{R}^{15\text{c}}$, $-\text{CH}_2\text{OC}(\text{O})\text{R}^{16\text{c}}$, $-\text{CH}_2\text{OC}(\text{O})\text{OR}^{17\text{c}}$ or $-\text{C}(\text{O})\text{OCH}_2\text{OR}^{18\text{c}}$;

$\text{R}^{8\text{c}}$, $\text{R}^{9\text{c}}$, $\text{R}^{10\text{c}}$, $\text{R}^{11\text{c}}$ and $\text{R}^{12\text{c}}$ each independently represent a hydrogen atom or a $\text{C}_1\text{-C}_6$ alkyl group;

5 $\text{R}^{13\text{c}}$ represents hydrogen, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_3\text{-C}_8$ cycloalkylmethyl, or $\text{R}^{13\text{c}}$ represents a $\text{C}_1\text{-C}_6$ alkyl group optionally substituted by at least one substituent selected from hydroxyl and $\text{C}_1\text{-C}_6$ alkoxy; and

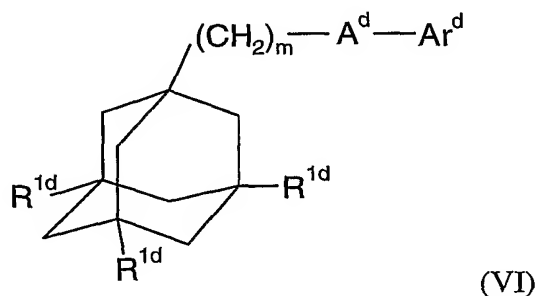
$\text{R}^{14\text{c}}$, $\text{R}^{15\text{c}}$, $\text{R}^{16\text{c}}$, $\text{R}^{17\text{c}}$ and $\text{R}^{18\text{c}}$ each independently represent a $\text{C}_1\text{-C}_6$ alkyl group;

10 with the proviso that when E^{c} is $\text{C}(\text{O})\text{NH}$, X^{c} is O, NH or $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})$, then $\text{R}^{5\text{c}}$ is other than a hydrogen atom or an unsubstituted $\text{C}_1\text{-C}_6$ alkyl group; or a pharmaceutically acceptable salt or solvate thereof.

Preferred compounds of formula (IV) are those wherein $\text{R}^{5\text{c}}$ represents an optionally substituted $\text{C}_1\text{-C}_6$ alkyl group, a preferred substituent being $-\text{Y}^{\text{c}}-\text{R}^{6\text{c}}$. When $\text{R}^{5\text{c}}$ is
15 substituted with a 5- or 6-membered heteroaromatic ring comprising from 1 to 4 heteroatoms, it is preferred that the number of heteroatoms in the ring is not greater than 2.

Compounds of formula (IV) are described in WO 01/44170.

20 In a fourth embodiment of the present invention the P2X_7 receptor antagonist is a compound of formula

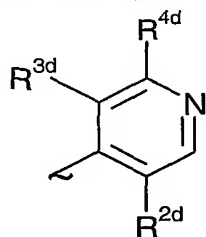


wherein m represents 1, 2 or 3;

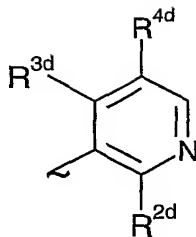
25 each $\text{R}^{1\text{d}}$ independently represents a hydrogen or halogen atom;

A^d represents $C(O)NH$ or $NHC(O)$;

Ar^d represents a group

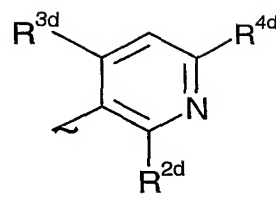


(VII)



(VIII)

or

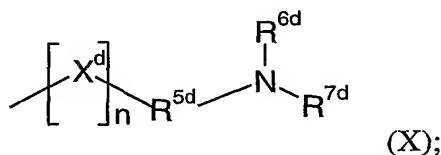


(IX)

;

- one of R^{2d} and R^{3d} represents halogen, nitro, amino, hydroxyl, or a group selected from (i) C_1 - C_6 alkyl optionally substituted by at least one halogen atom, (ii) C_3 - C_8 cycloalkyl, (iii) C_1 - C_6 alkoxy optionally substituted by at least one halogen atom, and (iv) C_3 - C_8 cycloalkyloxy, and the other of R^{2d} and R^{3d} represents a hydrogen or halogen atom;

R^{4d} represents a group



(X);

X^d represents an oxygen or sulphur atom or a group $>N-R^{8d}$;

n is 0 or 1;

R^{5d} represents a C_1 - C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy;

R^{6d} and R^{7d} each independently represent a hydrogen atom, C_1 - C_6 alkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen, C_1 - C_6 alkoxy, and (di)- C_1 - C_4 alkylamino (itself optionally substituted by at least one hydroxyl group)), or C_3 - C_8 cycloalkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy); and

R^{8d} represents a hydrogen atom or a C_1 - C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy;

with the provisos that:

(a) when n is 0, then A^d is $NHC(O)$, and

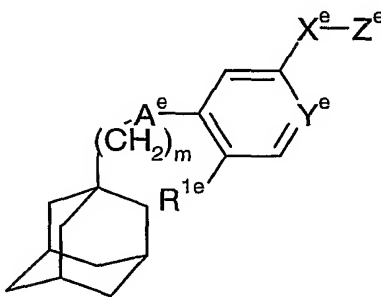
(b) when n is 1, X^d represents oxygen and A^d is $C(O)NH$, then R^{6d} and R^{7d} do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1 - C_6 alkyl, or when one of R^{6d} and R^{7d} represents a hydrogen atom, then the other of R^{6d} and R^{7d} does not represent an unsubstituted C_1 - C_6 alkyl; and

(c) when n is 1, X^d is oxygen, sulphur or $>NH$ and A^d is $NHC(O)$, then R^{6d} and R^{7d} do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1 - C_6 alkyl, or when one of R^{6d} and R^{7d} represents a hydrogen atom, then the other of R^{6d} and R^{7d} does not represent an unsubstituted C_1 - C_6 alkyl or $-CH_2CH_2OH$;

or a pharmaceutically acceptable salt or solvate thereof.

Compounds of formula (VI) are described in WO 03/41707.

In another aspect of the present invention the $P2X_7$ receptor antagonist is a compound of formula



(XI)

wherein m represents 1, 2 or 3;

A^e represents $C(O)NH$ or $NHC(O)$;

Y^e represents N or CH;

X^e represents a bond, CO, $(CH_2)_{1-6}$, $O(CH_2)_{1-6}$, $(CH_2)_{1-6}NH(CH_2)_{1-6}$, $(CH_2)_{1-6}O(CH_2)_{1-6}$,

$NH(CH_2)_{1-6}$;

Z^e represents $NR^{2e}R^{3e}$;

R^{1e} represents halogen, cyano, nitro, amino, hydroxyl, C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl, which alkyl or cycloalkyl group can be optionally substituted by one or more fluorine atoms;

- 5 R^{2e} and R^{3e} each independently represent a hydrogen atom, C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl, which alkyl or cycloalkyl group can be optionally substituted by one or more groups selected from hydroxyl, halogen or C_1 - C_6 alkoxy, or R^{2e} and R^{3e} together with the nitrogen atom to which they are attached form a 3- to 9-membered saturated mono- or bicyclic heterocyclic ring comprising from 1 to 2 nitrogen
10 atoms and optionally an oxygen atom, which heterocyclic ring can be optionally substituted by one or more groups selected from hydroxyl, halogen or C_1 - C_6 alkoxy; or a pharmaceutically acceptable salt or solvate thereof.

- 15 Compounds of formula (XI) may be prepared by chemistry according or analogous to that described in the references cited herein above.

In a further aspect of the present invention the P2X₇ receptor antagonist is:-

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

- 20 2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

(*R*)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

- 25 2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5 2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

10 2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

15 5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[(1*R*)-2-hydroxy-1-methylethyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridinecarboxamide,

5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

20 5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[(2*S*)-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

25 *N*-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

or a pharmaceutically acceptable salt or solvate of any one thereof.

Pharmaceutically acceptable salts include, where applicable, acid addition salts derived from pharmaceutically acceptable inorganic and organic acids such as a chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2-

30

or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballoylate, hydroxynaphthalene-carboxylate or oleate salt; and salts prepared from pharmaceutically acceptable inorganic and organic bases. Salts derived from inorganic bases include
 5 aluminium, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and bismuth salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary and tertiary amines, cyclic amines like arginine, betaine, choline and the like. Examples of
 10 pharmaceutically acceptable solvates include hydrates.

Examples of P2X₇ receptor antagonists that may be used in the present invention include:-

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, dihydrochloride

15 2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide, hydrochloride

(R)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate (1:1) salt
 20

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide, hydrochloride

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate (1:1) salt
 25

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride
 30

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

2-Chloro-5-piperazin-1-ylmethyl-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide, dihydrochloride

5 2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide, hydrochloride

2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

10 5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[[*(1R)*-2-hydroxy-1-methylethyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridinecarboxamide,

15 5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide, hydrochloride

5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide, hydrochloride

5-Chloro-2-[3-[[*(2S)*-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide, dihydrochloride, and

20 *N*-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride.

The P2X₇ receptor antagonist used in the present invention may be capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric
25 and optical isomers of the active ingredient and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The second active ingredient in the product or kit of the present invention is a tumour necrosis factor α (TNF α) inhibitor. A TNF α inhibitor is a compound or other substance
30 that is capable of inhibiting TNF α activity, whether fully or partially. A detailed

description of compounds or substances that may be used in the present invention as TNF α inhibitors can be found, for example, in published International patent application no. WO 98/05357, the entire contents of which are incorporated herein by reference.

5 In an embodiment of the invention the tumour necrosis factor α (TNF α) inhibitor is a receptor molecule capable of binding to TNF α . Such receptor molecules are known in the art and a detailed description of receptor molecules that may be used in the present invention can be found, for example, on pages 32 to 35 of WO 98/05357. An example of a receptor molecule that gives especially good results in the present invention is Etanercept
10 (*Expert Opin. Pharmacother.* (2001) 2(7); 1137-1148). Etanercept is a fusion protein consisting of the extracellular ligand-binding portion of the human tumor necrosis factor receptor linked to the Fc portion of human IgG. It is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. Etanercept is considered to attenuate the biological activity of the pro-inflammatory
15 cytokine tumor necrosis factor (TNF) by binding the protein and blocking its interaction with cell surface TNF receptors. Etanercept is marketed by Amgen and Wyeth Pharmaceuticals under the tradename 'Enbrel'. A further example of a TNF α inhibitor that is a receptor molecule and that may be used in accordance with the present invention is Pegsunercept, a PEGylated soluble TNF α inhibitor receptor (*Arth. Rheum.* (2003) 48,
20 *S121*).

In another embodiment of the invention, the tumour necrosis factor α (TNF α) inhibitor is an anti-TNF α antibody. Examples of anti-TNF antibodies according to the present invention include monoclonal, chimeric, humanized, resurfaced and recombinant
25 antibodies and fragments thereof that are capable of inhibiting TNF α activity, whether fully or partially. Such antibodies are known in the art and are described, for example, on pages 13 to 32 of WO 98/05357. Specific examples of anti-TNF α antibodies that may be used in the present invention are monoclonal antibodies Infliximab and Adalimumab (D2E7). Infliximab is a chimeric IgG1k monoclonal antibody composed of human constant
30 and murine variable regions and is marketed by Centocor under the tradename 'Remicade'.

Adalimumab (D2E7) is a recombinant human IgG1 monoclonal antibody prepared using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:k constant regions. Adalimumab (D2E7) is marketed by Abbott Laboratories under the tradename 'Humira'. A further example of an anti-TNF α antibody fragment that may be used in accordance with the present invention is CDP-870, a PEGylated humanized antibody fragment that binds with high affinity to TNF α (*Cur. Opin. Investig. Drugs.* (2003) 4; 588-592).

In a further embodiment of the invention, the tumour necrosis factor α (TNF α) inhibitor may bind the TNF α receptor and includes anti-TNF α receptor antibodies.

It has been found that the choice of active ingredients according to the invention is advantageous because it results in a beneficial anti-inflammatory effect and, accordingly, can be used to treat various acute and chronic inflammatory conditions/disorders such as rheumatoid arthritis. Treatment of inflammatory disorders may involve a reduction in swelling and/or alleviation of pain associated with the condition. In this regard the products of the present invention have proven especially beneficial in lowering or alleviating pain caused by inflammatory disorders, in particular rheumatoid arthritis.

A further advantageous aspect of the present invention is that it may allow effective treatment using lower doses of TNF α inhibitor than is possible using a TNF α inhibitor alone. This is significant as use of biological therapeutic agents such as TNF α inhibitors can leave patients susceptible to opportunistic infections. Moreover, established anti-TNF α therapies such as Etanercept have the added complication that they have a long "wash-out" period before the drug is removed from the system. Co-administration with a P2X₇ antagonist that allows the dose of TNF α inhibitor to be lowered without compromising efficacy reduces these safety concerns and potentially allows anti-TNF α therapies to be applied to patient populations where their use has to date been considered inappropriate.

In a preferred embodiment of the present invention, the second active ingredient is the tumour necrosis factor α (TNF α) inhibitor Etanercept and the first active ingredient which is a P2X₇ receptor antagonist is selected from

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-*N*-
5 (tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-
benzamide,

(*R*)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-*N*-
(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

10 2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-
ylmethyl)-benzamide,

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-
ylmethyl)benzamide,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-
15 ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-
ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-
ylmethyl)-benzamide,

20 2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-
ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-
(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

25 2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-*N*-(tricyclo[3.3.1.1]dec-1-
ylmethyl)-benzamide,

2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-
30 ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[[*(1R)*-2-hydroxy-1-methylethyl]amino]propyl]-*N*-
(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridinecarboxamide,

5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-
pyridinecarboxamide,

5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-
4-pyridinecarboxamide,

5-Chloro-2-[3-[[*(2S)*-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-
ylmethyl)-4-pyridinecarboxamide,

N-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-
tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

or a pharmaceutically acceptable salt or solvate of any one thereof. The products of this
embodiment may in particular be used to reduce or alleviate pain caused by inflammatory
disorders, especially rheumatoid arthritis.

15 The first and second active ingredients are administered simultaneously (other than in
admixture), sequentially or separately to treat inflammatory conditions. By sequential is
meant that the first and second active ingredients are administered, in any order, one
immediately after the other. They still have the desired effect if they are administered
separately.

20

The first and second active ingredients are conveniently administered by oral or parenteral
(e.g. intravenous, subcutaneous, intramuscular, intraarticular or inhaled) administration
using conventional systemic dosage forms, such as tablets, capsules, pills, powders,
aqueous or oily solutions or suspensions, emulsions and sterile injectable aqueous or oily
25 solutions or suspensions. These dosage forms will usually include one or more
pharmaceutically acceptable ingredients which may be selected, for example, from
adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents,
emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings and
colorants. As will be understood by those skilled in the art, the most appropriate method of
30 administering the active ingredients is dependent on a number of factors. However, in

general, oral administration of the first active ingredient is preferred, whilst subcutaneous administration of the second active ingredient is preferred.

For the above-mentioned therapeutic uses the dosages administered will, of course, vary with the first and second active ingredients employed, the mode of administration, the treatment desired and the condition or disorder indicated. However, in general, satisfactory results will be obtained when the total, combined, dosage of first and second active ingredients is in the range from 10 to 2000 milligrammes (mg), particularly from 10, 20, 30, 40, 50, 100, 150, 200 or 300 to 1800, 1500, 1200, 1000, 800, 600, 500 or 400 mg.

The pharmaceutical product or kit of the invention may be administered as divided doses. When administered by divided doses the first and second ingredients may be administered at a different frequency from one another. However, in general, frequency of administration of each of the active ingredients will independently be in the range of from one dose every 7 days to 4 doses a day

In an embodiment of the present invention the dosage of the first active ingredient in the pharmaceutical product or kit is in the range of from 5 to 1000 mg, preferably from 20, 50, 100, or 200, to 800, 600, 500 or 400 mg per day, which daily dose may be administered as divided doses from 1 to 4 times a day, preferably once or twice a day; whilst the dose of the second active ingredient is in the range of from 1 to 100 mg, preferably from 5, 10, or 20 to 80, 50 or 40 mg, which dose is administered at a frequency in the range of from one dose every 7 days to one dose daily. The dosing routine of this embodiment may in particular be used when the first active ingredient is delivered by oral administration or inhalation and the second active ingredient is administered by subcutaneous injection. Subcutaneous injection of the second active ingredient and the dosing regime of this embodiment may in particular be employed when the second active ingredient is Etanercept.

The present invention further provides the use of a pharmaceutical product or kit according to the invention in the manufacture of a medicament for the treatment of an inflammatory disorder.

5 Still further, the present invention provides a method of treating an inflammatory disorder which comprises simultaneously, sequentially or separately administering:

(a) a (therapeutically effective) dose of a first active ingredient which is a P2X₇ receptor antagonist which P2X₇ receptor antagonist is an adamantyl derivative; and

(b) a (therapeutically effective) dose of a second active ingredient which is a tumour
10 necrosis factor α (TNF α) inhibitor,
to a patient in need thereof.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and
15 "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the condition or disorder in question. Persons at risk of developing a particular condition or
20 disorder generally include those having a family history of the condition or disorder, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition or disorder.

The invention further relates to triple combination therapies for the treatment of any one of
25 rheumatoid arthritis, osteoarthritis, osteoporosis, psoriasis, inflammatory bowel diseases, COPD, asthma, allergic rhinitis or cancer or the neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease or stroke.

For the treatment of rheumatoid arthritis, the pharmaceutical product or kit of the invention
30 may be combined with "biological agents" such as IL-1 receptor antagonists (e.g.

Anakinra) and IL-1 trap, IL-18 receptor, anti-IL-6 Ab, anti-CD20 Ab, anti-IL-15 Ab and CTLA4Ig.

Suitable agents to be used in combination with the pharmaceutical product or kit of the invention include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin. Cyclo-oxygenase inhibiting nitric oxide donors (CINOD's) and "disease modifying agents" (DMARDs) such as cyclosporine A, leflunomide; ciclesonide; hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold may also be used.

The present invention still further relates to the combination of a pharmaceutical product or kit of the invention together with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist selected from the group consisting of zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; N-(5-substituted)-thiophene-2-alkylsulfonamides; 2,6-di-tert-butylphenol hydrazones; methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; pyridinyl-substituted 2n cyanonaphthalene compounds such as L-739,010; 2-cyanoquinoline compounds such as L-746,530; indole and quinoline compounds such as MK-591, MK-886, and BAY x 1005.

The present invention still further relates to a pharmaceutical product or kit of the invention together with a receptor antagonist for leukotrienes LTB₄, LTC₄, LTD₄, and LTE₄ selected from the group consisting of the phenothiazin-3-ones such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to a pharmaceutical product or kit of the invention together with a PDE4 inhibitor including inhibitors of the isoform PDE4D.

The present invention still further relates to a pharmaceutical product or kit of the invention together with a antihistaminic H₁ receptor antagonists including cetirizine,
5 loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine.

The present invention still further relates to a pharmaceutical product or kit of the invention together with a gastroprotective H₂ receptor antagonist or the proton pump
10 inhibitors (such as omeprazole)

The present invention still further relates to a pharmaceutical product or kit of the invention together with an α_1 - and α_2 -adrenoceptor agonist vasoconstrictor sympathomimetic agent, including propylhexedrine, phenylephrine, phenylpropanolamine,
15 pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride.

The present invention still further relates to a pharmaceutical product or kit of the invention together with anticholinergic agents including ipratropium bromide; tiotropium
20 bromide; oxitropium bromide; pirenzepine; and telenzepine.

The present invention still further relates to a pharmaceutical product or kit of the invention together with methylxanthanines including theophylline and aminophylline;
25 sodium cromoglycate; or muscarinic receptor (M1, M2, and M3) antagonist.

The present invention still further relates to a pharmaceutical product or kit of the invention together with a modulators of chemokine receptor function such as CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX₃CR1 for the C-X₃-C family.

The present invention still further relates to a pharmaceutical product or kit of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

The present invention still further relates to a pharmaceutical product or kit of the invention together with (a) tryptase inhibitors; (b) platelet activating factor (PAF) antagonists; (c) interleukin converting enzyme (ICE) inhibitors; (d) IMPDH inhibitors; (e) adhesion molecule inhibitors including VLA-4 antagonists; (f) cathepsins; (g) glucose-6 phosphate dehydrogenase inhibitors; (h) kinin-B₁ - and B₂ -receptor antagonists; (i) anti-gout agents, e.g., colchicine; (j) xanthine oxidase inhibitors, e.g., allopurinol; (k) uricosuric agents, e.g., probenecid, sulfinpyrazone, and benzbromarone; (l) growth hormone secretagogues; (m) transforming growth factor (TGF β); (n) platelet-derived growth factor (PDGF); (o) fibroblast growth factor, e.g., basic fibroblast growth factor (bFGF); (p) granulocyte macrophage colony stimulating factor (GM-CSF); (q) capsaicin cream; (r) Tachykinin NK₁ and NK₃ receptor antagonists selected from the group consisting of NKP-608C; SB-233412 (talnetant); and D-4418; and (s) elastase inhibitors selected from the group consisting of UT-77 and ZD-0892 (t) induced nitric oxide synthase inhibitors (iNOS) or (u) chemoattractant receptor-homologous molecule expressed on TH2 cells, (CRTH2 antagonists).

The pharmaceutical product or kit of the invention may also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin,

5 sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, induced nitric oxide synthase inhibitors (iNOS inhibitors), and the cyclo-oxygenase inhibiting nitric oxide donors (CINOD's) analgesics (such as paracetamol and tramadol), cartilage sparing agents such as diacerein, doxycycline and glucosamine, and hyaluronic acids such as hyalgan and synvisc.

10 The pharmaceutical product or kit of the invention may also be used in combination with existing therapeutic agents for the treatment of inflammatory bowel diseases (Ulcerative colitis and Crohn's disease). Suitable agents to be used include 5-amino-salicylates, the thiopurines, azathioprine and 6-mecaptopurine.

15 The pharmaceutical product or kit of the invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and farnesyl transferase inhibitors, VegF inhibitors, and antimetabolites such as antineoplastic agents, especially antimitotic drugs including the vinca alkaloids such as vinblastine and vincristine.

20 The pharmaceutical product or kit of the invention may also be used in combination with antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antiseptics compounds such as Valant.

25 The pharmaceutical product or kit of the invention may also be used in combination with calcium channel blockers, lipid lowering agents such as fibrates, beta-blockers, ACE inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

30 The pharmaceutical product or kit of the invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, COMT inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide

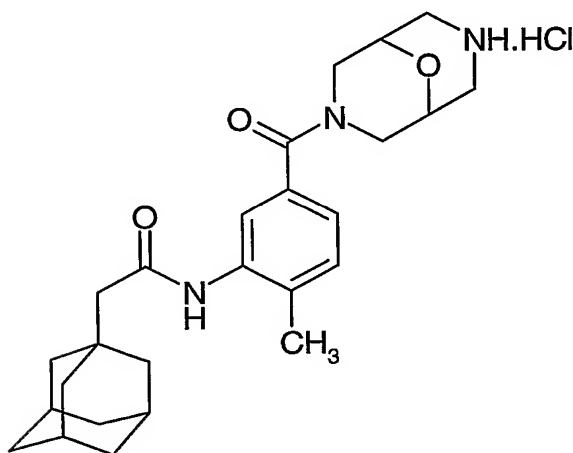
synthase), and anti Alzheimer's drugs such as donepezil, tacrine, propentofylline or metryfonate.

The pharmaceutical product or kit of the invention may also be used in combination with osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax and immunosuppressant agents such as FK-506, rapamycin, cyclosporine, and azathioprine.

The present invention will now be further understood by reference to the following illustrative examples.

The following P2X₇ antagonists were employed in the examples:-

1. *N*-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride



P2X₇ antagonist **1**. (*N*-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride) was prepared as follows.

a) 3-(4-Methyl-3-nitrobenzoyl)-7-(phenylmethyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane

Oxalyl chloride (9.6ml) in dichloromethane (30ml) was added dropwise over 45 minutes to an ice-cooled solution of 4-methyl-3-nitro-benzoic acid (10.0g) in dichloromethane (320ml) containing DMF (0.1ml). The reaction mixture was stirred at room temperature for 1 hour then concentrated *in vacuo*. The acid chloride was taken into THF (320ml) and cooled in an ice-bath before adding *N,N*-diisopropylethylamine (38ml) then 3-(phenylmethyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane, dihydrochloride (16.0g) (prepared as described in WO 01/028992) portionwise. The reaction was stirred for 18 hours then diluted with ethyl acetate (600ml) and washed with water (2x200ml) and saturated sodium bicarbonate (aq) (3x150ml) then dried (MgSO₄), filtered and concentrated to afford the sub-titled compound (18.5g).

$m/z = 382$

b) 3-(3-Amino-4-methylbenzoyl)-7-(phenylmethyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane

Reduced iron powder (7.9g) was added over 15 minutes to a stirred solution of the product of step a) (18.0g) and ammonium chloride (7.5g) in ethanol/water (3:1, 320ml) at 70°C. The reaction mixture was heated at reflux for 2 hours then filtered and concentrated *in vacuo*. The residue was taken into ethyl acetate (400ml), washed with water (2x150ml) then the organic phase dried (MgSO₄) and concentrated *in vacuo* to afford the sub-title compound (14.5g).

$m/z = 352$

c) *N*-[2-Methyl-5-[[7-(phenylmethyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]carbonyl]phenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide

Prepared by the method of step a) using 1-adamantaneacetic acid and the product of step b). Recrystallisation (ethyl acetate) afforded the sub-title compound.

m/z 528

**d) N-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-
tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**

4M HCl in 1,4-dioxane (8ml) was added to a solution of the product of step c) (13.0g) in ethyl acetate (300ml). The resulting precipitate was isolated by filtration then suspended in ethanol (300ml) and 5% palladium on carbon (1.2g) added. The reaction mixture was stirred under 3 atmospheres pressure of hydrogen for 36 hours. Methanol was then added under an atmosphere of nitrogen, then the catalyst removed by filtration and the filtrate concentrated *in vacuo*. Recrystallisation (isopropanol: methanol 25:1, 800ml) gave the title compound (9.1g).

m/z 438 (M+H)⁺

δ_H (400MHz, d₆-DMSO, Me₄Si, 90°C) 9.06 (1H, s), 7.64 (1H, s), 7.25 (1H, m), 7.19 (1H, m), 4.15 (2H, s), 3.96 (2H, d, *J* 14Hz), 3.35-3.23 (6H, m), 2.26 (3H, s), 2.14 (2H, s), 1.96 (3H, br s), 1.69-1.62 (12H, m).

Example 1

Pharmacological analysis to determine the effect of TNF α inhibitor / P2X₇ antagonist combinations (without addition of a P2X₇ agonist).

Human peripheral blood monocytes were prepared from the blood of healthy human volunteers collected in EDTA blood tubes. Monocytes were isolated by serial gradient centrifugation and washing to produce a pure population of cells. Lipopolysaccharide (LPS) was then added to the cell suspension in tissue culture and this was incubated for 4 - 12 hours at 37 degrees centigrade. TNF α inhibitor and / or a P2X₇ antagonist or vehicle

was then added to the cells. After incubation, samples of cell supernatants were transferred to a 96-well plate for subsequent cytokine and mediator measurements. The formation of inflammatory mediators was measured in the cell supernatants by specific ELISA assays for the cytokines IL-1, IL-18, TNF α and for other mediators including PGE2, NO and matrix metalloproteinases (MMPs). The levels of mediators released in the presence of a P2X₇ receptor antagonist alone, or in the presence of TNF α inhibitor alone, or in the presence of a combination of a P2X₇ receptor antagonist with TNF α inhibitor were determined. The effects of the antagonists / TNF α inhibitor alone and in combination were then compared. Statistically significant levels of inhibitory activity against a single mediator (IL-1 or TNF α) or on multiple mediators by P2X₇ antagonist / TNF α inhibitor combinations, in comparison to that achieved by either a P2X₇ antagonist or TNF α inhibitor alone, is an indicator for increased efficacy in the treatment of disease.

Example 2

Pharmacological analysis to determine the effect of TNF α inhibitor / P2X₇ antagonist combinations (with addition of a P2X₇ agonist).

Human peripheral blood monocytes were prepared from the blood of healthy human volunteers collected in EDTA blood tubes. Monocytes were isolated by serial gradient centrifugation and washing to produce a pure population of cells. Lipopolysaccharide (LPS) was then added to the cell suspension in tissue culture and this was incubated for 4 - 12 hours at 37 degrees centigrade. Test mixtures were then added followed by the addition of the P2X₇ receptor agonist BzATP. Test mixtures can comprise of vehicle as control, a P2X₇ receptor antagonist, or a combination of a P2X₇ receptor antagonist together with TNF α inhibitor. After incubation, samples of cell supernatants were transferred to a 96-well plate for subsequent cytokine and mediator measurements. The formation of inflammatory mediators was measured in the cell supernatants by specific ELISA assays for the cytokines IL-1, IL-18, TNF α and for other mediators including PGE2, NO and matrix metalloproteinases (MMPs). The levels of mediators released in the presence of a P2X₇ receptor antagonist alone, or in the presence of a combination of a

P2X₇ receptor antagonist with TNF α inhibitor were determined. The effects produced by a P2X₇ antagonist alone and in combination with TNF α inhibitor were then compared. Statistically significant levels of inhibitory activity against a single mediator (IL-1 or TNF α) or on multiple mediators by P2X₇ antagonist / TNF α inhibitor combinations in
5 comparison to that achieved by a P2X₇ antagonist alone is an indicator for increased efficacy in the treatment of disease.

Example 3

Assessment of anti-inflammatory activity of TNF α inhibitor / P2X₇ antagonist combinations in rat Streptococcal cell wall-induced arthritis.¹
10

Streptococcal cell wall (SCW)-induced arthritis was induced in the left ankle of female Lewis rats. Animals were sensitised by intra-articular injection of 5 μ g (in 20 μ L) SCW (Lee Laboratories) into the left ankle. Ankle swelling was assessed 3 days after injection
15 and non-responders (animals with no apparent ankle swelling) were rejected. Responding animals were randomly allocated to the test groups.

Arthritis was induced 21 days after sensitisation by intravenous (iv) injection of SCW (100 μ g in 500 μ L saline). Animals were monitored and assessed on a daily basis through
20 to termination 6 days after induction. The rats were housed on sawdust and provided with food and water *ad libitum*.

In this example the P2X₇ antagonist 1, was orally dosed at 30mg/kg (4 mL/kg, bid). The compound was dosed as a suspension in 1% (w/v) methylcellulose in deionised water and
25 was freshly prepared on a daily basis. Dosing commenced 1 day prior to induction of arthritis and continued through to termination on day 6 post-induction. Etanercept (0.5 mg/kg) was administered by subcutaneous injection (1 mL/kg) 1 day prior to induction of arthritis and then on days 1, 3 and 5 post-induction.

Ankle diameters were measured with vernier callipers on a daily basis from day -1. Mechanical thresholds were assessed using von Frey filaments on days -1, 1, 3 and 5. The filaments were applied in increasing weights to the ankle region on the footpad of both feet. The first filament to induce a withdrawal response was considered to be the threshold.

Effects on ankle swelling and mechanical threshold were calculated on an area under the curve (AUC) basis, as the sum of the differences from individual day -1 values. The size and direction of the interaction was calculated and data analysis performed by ANOVA followed by Dunnett's test on the AUC data (SAS version 8.01). Results are summarised in the Table below:

	% reduction of AUC (compared to arthritic vehicle control)	
	Ankle swelling	Von Frey threshold
P2X ₇ antagonist 1	28.5 ± 13.5	21.1 ± 10.9
Etanercept	44.0 ± 4.7*	7.4 ± 6.8
P2X ₇ antagonist 1 + Etanercept	47.5 ± 4.7*	67.4 ± 13.7** Test of interaction p=0.085***

*p<0.01, **p<0.001 vs arthritic vehicle control,

*** an interaction score indicating a greater than additive benefit for the combination.

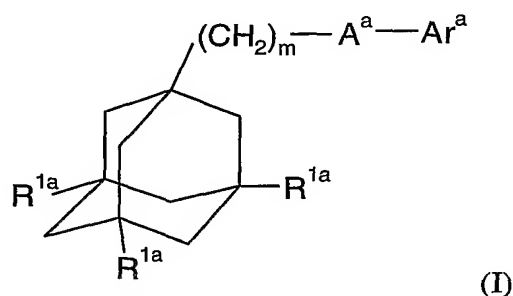
From the above results it can be seen that the combination of the P2X₇ antagonist 1 and Etanercept showed a positive interaction to produce a significantly greater reduction in mechanical threshold than could be expected based on their use alone. The finding that the two drugs have a positive effect on von Frey threshold in a combination which shows no additional benefit on ankle swelling indicates that this combination of drugs has a profound and unexpectedly positive effect on inflammatory joint pain.

1. Experimental procedure based on that described by Carlson RP, Jacobsen PB;
'Comparison of adjuvant and streptococcal cell wall-induced arthritis in the rat' in Morgan
DW, Marshall LA, editors; *In Vivo Models of Inflammation*. Basel: Birkhauser Verlag;
1999.

CLAIMS

1. A pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a P2X₇ receptor antagonist which P2X₇ receptor antagonist is an
 5 adamantyl derivative, and a preparation of a second active ingredient which is a tumour necrosis factor α (TNF α) inhibitor, for simultaneous, sequential or separate use in therapy.

2. A composition according to claim 1 wherein the P2X₇ receptor antagonist is a compound of formula

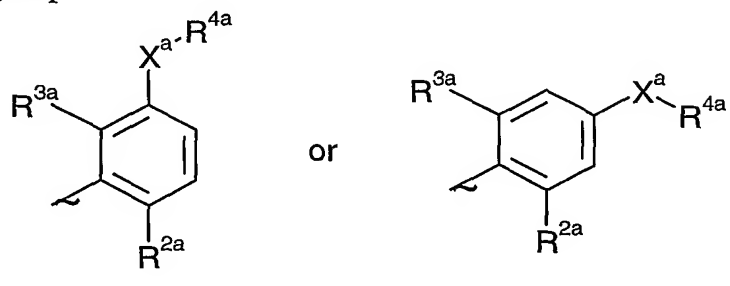


wherein m represents 1, 2 or 3;

each R^{1a} independently represents a hydrogen or halogen atom;

15 A^a represents C(O)NH or NHC(O);

Ar^a represents a group



X^a represents a bond, an oxygen atom or a group CO, (CH₂)₁₋₆, CH=, (CH₂)₁₋₆O,

O(CH₂)₁₋₆, O(CH₂)₂₋₆O, O(CH₂)₂₋₃O(CH₂)₁₋₃, CR'(OH), (CH₂)₁₋₃O(CH₂)₁₋₃,

20 (CH₂)₁₋₃O(CH₂)₂₋₃O, NR^{5a}, (CH₂)₁₋₆NR^{5a}, NR^{5a}(CH₂)₁₋₆, (CH₂)₁₋₃NR^{5a}(CH₂)₁₋₃,
 O(CH₂)₂₋₆NR^{5a}, O(CH₂)₂₋₃NR^{5a}(CH₂)₁₋₃, (CH₂)₁₋₃NR^{5a}(CH₂)₂₋₃O, NR^{5a}(CH₂)₂₋₆O,

$\text{NR}^{5a}(\text{CH}_2)_{2-3}\text{O}(\text{CH}_2)_{1-3}$, CONR^{5a} , NR^{5a}CO , $\text{S}(\text{O})_n$, $\text{S}(\text{O})_n\text{CH}_2$, $\text{CH}_2\text{S}(\text{O})_n$, $\text{SO}_2\text{NR}^{5a}$ or $\text{NR}^{5a}\text{SO}_2$;

n is 0, 1 or 2;

R' represents a hydrogen atom or a C_1 - C_6 alkyl group;

5 one of R^{2a} and R^{3a} represents a halogen, cyano, nitro, amino, hydroxyl, or a group selected from (i) C_1 - C_6 alkyl optionally substituted by at least one C_3 - C_6 cycloalkyl, (ii) C_3 - C_8 cycloalkyl, (iii) C_1 - C_6 alkyloxy optionally substituted by at least one C_3 - C_6 cycloalkyl, and (iv) C_3 - C_8 cycloalkyloxy, each of these groups being optionally substituted by one or more fluorine atoms, and the other of R^{2a} and R^{3a} represents a
10 hydrogen or halogen atom;

either R^{4a} represents a 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system containing one or two nitrogen atoms and optionally an oxygen atom, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, carboxyl, cyano, C_1 - C_6 alkyl,

15 C_1 - C_6 hydroxyalkyl, $-\text{NR}^{6a}\text{R}^{7a}$, $-(\text{CH}_2)_r\text{NR}^{6a}\text{R}^{7a}$ and $-\text{CONR}^{6a}\text{R}^{7a}$, or R^{4a} represents a 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from $-\text{NR}^{6a}\text{R}^{7a}$, $-(\text{CH}_2)_r\text{NR}^{6a}\text{R}^{7a}$ and $-\text{CONR}^{6a}\text{R}^{7a}$, the ring system being optionally further substituted by one or more substituents independently selected from fluorine atoms, hydroxyl and C_1 - C_6 alkyl;

20 r is 1, 2, 3, 4, 5 or 6;

R^{5a} represents a hydrogen atom or a C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl group;

R^{6a} and R^{7a} each independently represent a hydrogen atom or a C_1 - C_6 alkyl, C_2 - C_6 hydroxyalkyl or C_3 - C_8 cycloalkyl group, or R^{6a} and R^{7a} together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic
25 ring;

with the provisos that,

(a) when A^a represents $\text{C}(\text{O})\text{NH}$ and R^{4a} represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X^a is other than a bond, and

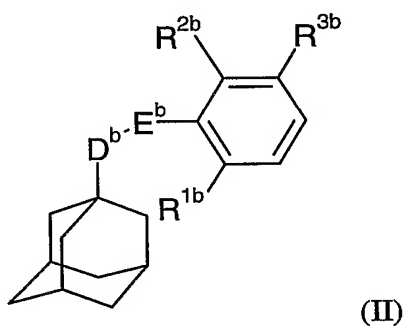
(b) when A^a represents $C(O)NH$ and X^a represents a group $(CH_2)_{1-6}$ or $O(CH_2)_{1-6}$, then R^{4a} does not represent an unsubstituted imidazolyl, unsubstituted morpholinyl, unsubstituted piperidinyl or unsubstituted pyrrolidinyl group, and

(c) when A^a represents $NHC(O)$ and R^{4a} represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X^a is other than a bond, and

(d) when A^a represents $NHC(O)$ and X^a represents $O(CH_2)_{1-6}$, $NH(CH_2)_{1-6}$ or SCH_2 , then R^{4a} does not represent an unsubstituted 1-piperidinyl or unsubstituted 1-pyrrolidinyl group, and

(e) when A^a represents $NHC(O)$ and X^a represents $O(CH_2)_{2-3}NH(CH_2)_2$, then R^{4a} does not represent an imidazolyl group;
or a pharmaceutically acceptable salt or solvate thereof.

3. A composition according to claim 1 wherein the $P2X_7$ receptor antagonist is a compound of formula

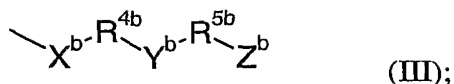


wherein D^b represents CH_2 or CH_2CH_2 ;

E^b represents $C(O)NH$ or $NHC(O)$;

R^{1b} and R^{2b} each independently represent a hydrogen or halogen atom, or an amino, nitro, C_1 - C_6 alkyl or trifluoromethyl group;

R^{3b} represents a group of formula



X^b represents an oxygen or sulphur atom or a group NH, SO or SO₂;

Y^b represents an oxygen or sulphur atom or a group NR^{11b}, SO or SO₂;

Z^b represents a group -OH, -SH, -CO₂H, C₁-C₆ alkoxy, C₁-C₆ alkylthio,

5 C₁-C₆-alkylsulphinyl, C₁-C₆-alkylsulphonyl, -NR^{6b}R^{7b}, -C(O)NR^{8b}R^{9b}, imidazolyl,

1-methylimidazolyl, -N(R^{10b})C(O)-C₁-C₆ alkyl, C₁-C₆ alkylcarbonyloxy,

C₁-C₆ alkoxy carbonyloxy, -OC(O)NR^{12b}R^{13b}, -OCH₂OC(O)R^{14b}, -OCH₂OC(O)OR^{15b}
or -OC(O)OCH₂OR^{16b};

R^{4b} represents a C₂-C₆ alkyl group;

10 R^{5b} represents a C₁-C₆ alkyl group;

R^{6b} , R^{7b} , R^{8b} , R^{9b} , R^{10b} , R^{12b} and R^{13b} each independently represent a hydrogen atom,
or a C₁-C₆ alkyl group optionally substituted by at least one hydroxyl group;

R^{11b} represents a hydrogen atom, or a C₁-C₆ alkyl group optionally substituted by at least
one substituent independently selected from hydroxyl and C₁-C₆ alkoxy; and

15 R^{14b} , R^{15b} and R^{16b} each independently represent a C₁-C₆ alkyl group;

with the provisos that (i) when E^b represents NHC(O), X^b represents O, S or NH and Y^b
represents O, then Z^b represents -NR^{6b}R^{7b} where R^{6b} represents a hydrogen atom and
 R^{7b} represents either a hydrogen atom or a C₁-C₆ alkyl group substituted by at least one

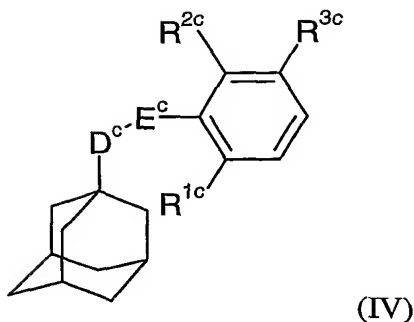
hydroxyl group, and (ii) when E^b represents NHC(O), X^b represents O, S or NH, Y

20 represents NH and R^{5b} represents CH₂CH₂, then Z^b is not -OH or imidazolyl;

or a pharmaceutically acceptable salt or solvate thereof.

4. A composition according to claim 1 wherein the P2X₇ receptor antagonist is a
compound of formula

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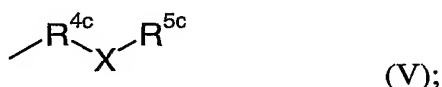


wherein D^c represents CH_2 or CH_2CH_2 ;

E^c represents $C(O)NH$ or $NHC(O)$;

R^{1c} and R^{2c} each independently represent hydrogen, halogen, amino, nitro, C_1 - C_6 alkyl or trifluoromethyl, but R^{1c} and R^{2c} may not both simultaneously represent hydrogen;

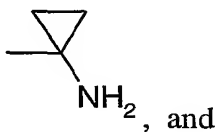
R^{3c} represents a group of formula



R^{4c} represents a C_1 - C_6 alkyl group;

X^c represents an oxygen or sulphur atom or a group NR^{13c} , SO or SO_2 ;

R^{5c} represents hydrogen, or R^{5c} represents C_1 - C_6 alkyl or C_2 - C_6 alkenyl, each of which may be optionally substituted by at least one substituent selected from halogen, hydroxyl, (di)- C_1 - C_6 -alkylamino, $-Y^c-R^{6c}$,



a 5- or 6-membered heteroaromatic ring comprising from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulphur which heteroaromatic ring may itself be optionally substituted by at least one substituent selected from halogen, hydroxyl and C_1 - C_6 alkyl;

Y^c represents an oxygen or sulphur atom or a group NH , SO or SO_2 ;

R^{6c} represents a group $-R^{7c}Z^c$ where R^{7c} represents a C_2 - C_6 alkyl group and Z^c represents an $-OH$, $-CO_2H$, $-NR^{8c}R^{9c}$, $-C(O)NR^{10c}R^{11c}$ or $-N(R^{12c})C(O)-C_1$ - C_6 alkyl group, and, in the case where Y^c represents an oxygen or sulphur atom or a group NH , R^{6c} additionally represents hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkylcarbonyl, C_1 - C_6

alkoxycarbonyl, $-\text{C}(\text{O})\text{NR}^{14\text{c}}\text{R}^{15\text{c}}$, $-\text{CH}_2\text{OC}(\text{O})\text{R}^{16\text{c}}$, $-\text{CH}_2\text{OC}(\text{O})\text{OR}^{17\text{c}}$ or $-\text{C}(\text{O})\text{OCH}_2\text{OR}^{18\text{c}}$;

$\text{R}^{8\text{c}}$, $\text{R}^{9\text{c}}$, $\text{R}^{10\text{c}}$, $\text{R}^{11\text{c}}$ and $\text{R}^{12\text{c}}$ each independently represent a hydrogen atom or a $\text{C}_1\text{-C}_6$ alkyl group;

5 $\text{R}^{13\text{c}}$ represents hydrogen, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_3\text{-C}_8$ cycloalkylmethyl, or $\text{R}^{13\text{c}}$ represents a $\text{C}_1\text{-C}_6$ alkyl group optionally substituted by at least one substituent selected from hydroxyl and $\text{C}_1\text{-C}_6$ alkoxy; and

$\text{R}^{14\text{c}}$, $\text{R}^{15\text{c}}$, $\text{R}^{16\text{c}}$, $\text{R}^{17\text{c}}$ and $\text{R}^{18\text{c}}$ each independently represent a $\text{C}_1\text{-C}_6$ alkyl group;

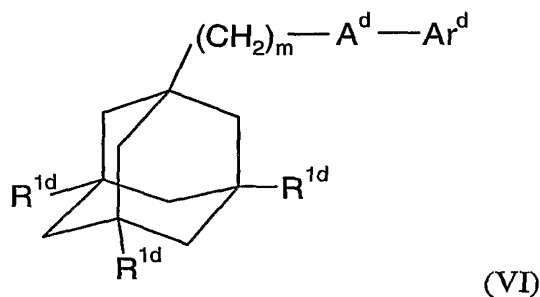
with the proviso that when E^{c} is $\text{C}(\text{O})\text{NH}$, X^{c} is O, NH or $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})$, then $\text{R}^{5\text{c}}$ is

10 other than a hydrogen atom or an unsubstituted $\text{C}_1\text{-C}_6$ alkyl group;

or a pharmaceutically acceptable salt or solvate thereof.

5. A composition according to claim 1 wherein the P2X_7 receptor antagonist is a compound of formula

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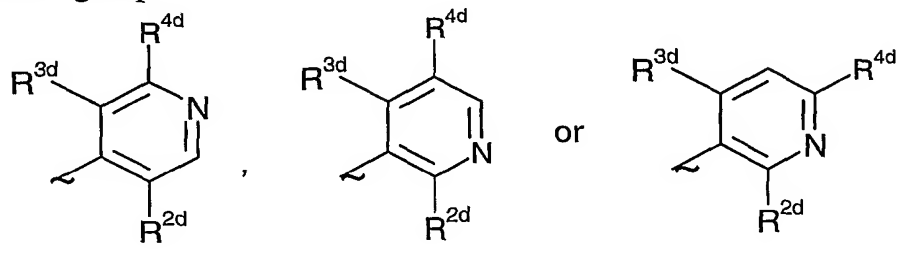


wherein m represents 1, 2 or 3;

each $\text{R}^{1\text{d}}$ independently represents a hydrogen or halogen atom;

20 A^{d} represents $\text{C}(\text{O})\text{NH}$ or $\text{NHC}(\text{O})$;

Ar^{d} represents a group

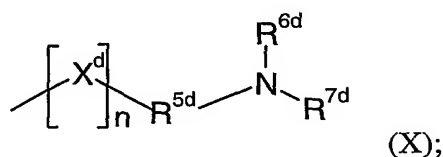


(VII)

(VIII)

(IX)

one of R^{2d} and R^{3d} represents halogen, nitro, amino, hydroxyl, or a group selected from (i) C_1 - C_6 alkyl optionally substituted by at least one halogen atom, (ii) C_3 - C_8 cycloalkyl, (iii) C_1 - C_6 alkoxy optionally substituted by at least one halogen atom, and (iv) C_3 - C_8 cycloalkyloxy, and the other of R^{2d} and R^{3d} represents a hydrogen or halogen atom;
 R^{4d} represents a group



X^d represents an oxygen or sulphur atom or a group $>N-R^{8d}$;

n is 0 or 1;

R^{5d} represents a C_1 - C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy;

R^{6d} and R^{7d} each independently represent a hydrogen atom, C_1 - C_6 alkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen, C_1 - C_6 alkoxy, and (di)- C_1 - C_4 alkylamino (itself optionally substituted by at least one hydroxyl group)), or C_3 - C_8 cycloalkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy); and

R^{8d} represents a hydrogen atom or a C_1 - C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy;

with the provisos that:

(d) when n is 0, then A^d is $NHC(O)$, and

(e) when n is 1, X^d represents oxygen and A^d is $C(O)NH$, then R^{6d} and R^{7d} do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1 - C_6 alkyl, or when one of R^{6d} and R^{7d} represents a hydrogen atom, then the other of R^{6d} and R^{7d} does not represent an unsubstituted C_1 - C_6 alkyl; and

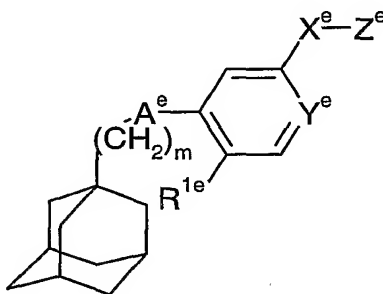
(f) when n is 1, X^d is oxygen, sulphur or $>NH$ and A^d is $NHC(O)$, then R^{6d} and R^{7d} do not both simultaneously represent a hydrogen atom or do not both

simultaneously represent an unsubstituted C₁-C₆ alkyl, or when one of R^{6d} and R^{7d} represents a hydrogen atom, then the other of R^{6d} and R^{7d} does not represent an unsubstituted C₁-C₆ alkyl or -CH₂CH₂OH;

or a pharmaceutically acceptable salt or solvate thereof.

5

6. A composition according to claim 1 wherein the P2X₇ receptor antagonist is a compound of formula



10

(XI)

wherein m represents 1, 2 or 3;

A^e represents C(O)NH or NHC(O);

Y^e represents N or CH;

15 X^e represents a bond, CO, $(CH_2)_{1-6}$, $O(CH_2)_{1-6}$, $(CH_2)_{1-6}NH(CH_2)_{1-6}$, $(CH_2)_{1-6}O(CH_2)_{1-6}$, $NH(CH_2)_{1-6}$;

Z^e represents $NR^{2e}R^{3e}$;

R^{1e} represents halogen, cyano, nitro, amino, hydroxyl, C₁-C₆ alkyl or C₃-C₈ cycloalkyl, which alkyl or cycloalkyl group can be optionally substituted by one or more

20 fluorine atoms;

R^{2e} and R^{3e} each independently represent a hydrogen atom, C₁-C₆ alkyl or C₃-C₈ cycloalkyl, which alkyl or cycloalkyl group can be optionally substituted by one or more groups selected from hydroxyl, halogen or C₁-C₆ alkoxy,

or R^{2e} and R^{3e} together with the nitrogen atom to which they are attached form a 3- to 9-
25 membered saturated mono- or bicyclic heterocyclic ring comprising from 1 to 2 nitrogen

atoms and optionally an oxygen atom, which heterocyclic ring can be optionally substituted by one or more groups selected from hydroxyl, halogen or C₁-C₆ alkoxy; or a pharmaceutically acceptable salt or solvate thereof.

5 7. A composition according to claim 1 wherein the P2X₇ receptor antagonist is:

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

10 (*R*)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide,

15 2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

20 2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

30 2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[[*(1R)*-2-hydroxy-1-methylethyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridinecarboxamide,

5 5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

10 5-Chloro-2-[3-[[*(2S)*-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

N-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

or a pharmaceutically acceptable salt or solvate of any one thereof.

15 8. A product according to any one of claims 1 to 7, wherein the second active ingredient is a receptor molecule capable of binding to TNF α .

9. A product according to claim 8 wherein the second active ingredient is Etanercept.

20 10. A product according to any one of claims 1 to 7, wherein the second active ingredient is an anti-TNF α antibody.

11. A product according to claim 10, wherein the second active ingredient is selected from Infliximab and Adalimumab (D2E7).

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12. A kit comprising a preparation of a first active ingredient which is a P2X₇ receptor antagonist which P2X₇ receptor antagonist is an adamantyl derivative, a preparation of a second active ingredient which is a tumour necrosis factor α (TNF α) inhibitor, and instructions for the simultaneous, sequential or separate administration of the preparations
30 to a patient in need thereof.

13. A kit according to claim 12 wherein the P2X₇ receptor antagonist is:

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5 2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

(*R*)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

10 2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

15 2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

20 2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

25 2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[[*(1R)*-2-hydroxy-1-methylethyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridinecarboxamide,

5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[[*(2S)*-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

N-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

or a pharmaceutically acceptable salt or solvate of any one thereof.

14. A kit according to any one of claims 12 to 13, wherein the second active ingredient is a receptor molecule capable of binding to TNF α .

15. A kit according to claim 14 wherein the second active ingredient is Etanercept.

16. A kit according to any one of claims 12 to 13, wherein the second active ingredient is an anti-TNF α antibody.

17. A kit according to claim 16, wherein the second active ingredient is selected from Infliximab and Adalimumab (D2E7).

18. Use of a pharmaceutical product or kit according to any one of the preceding claims in the manufacture of a medicament for the treatment of an inflammatory disorder.

19. Use according to claim 19, wherein the inflammatory disorder is rheumatoid arthritis.

20. A method of treating an inflammatory disorder which comprises simultaneously, sequentially or separately administering:

(a) a (therapeutically effective) dose of a first active ingredient which is a P2X₇ receptor antagonist which P2X₇ receptor antagonist is an adamantyl derivative; and

(b) a (therapeutically effective) dose of a second active ingredient which is a tumour necrosis factor α (TNF α) inhibitor,

5 to a patient in need thereof.

21. A method according to claim 20, wherein the inflammatory disorder is rheumatoid arthritis.

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 45/06, A61K 31/165, A61K 31/465, A61P 29/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, EPO-INTERNAL, PAJ, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1310493 A1 (PFIZER PRODUCTS), 14 May 2003 (14.05.2003), see paragraph [0100] --	1-21
X	WO 03042191 A1 (PFIZER PRODUCTS), 22 May 2003 (22.05.2003), page 40, line 13 - line 18 --	1-21
A	WO 03041707 A1 (ASTRAZENECA AB), 22 May 2003 (22.05.2003) --	1-21
A	WO 0144170 A1 (ASTRAZENECA AB), 21 June 2001 (21.06.2001) --	1-21

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 Sept 2004

Date of mailing of the international search report

23 -09- 2004

Name and mailing address of the ISA/

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0142194 A1 (ASTRAZENECA AB), 14 June 2001 (14.06.2001) --	1-21
A	WO 0061569 A1 (ASTRAZENECA AB), 19 October 2000 (19.10.2000) -- -----	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000817

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **20-21**
because they relate to subject matter not required to be searched by this Authority, namely:
see extra sheet
2. ☒ Claims Nos.: **1, 8, 12**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see extra sheet
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Box II.1

Claims 20-21 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

Box II.2

Present claims 1, 8, 12 relate to a composition comprising compounds where the compounds are defined by reference to a desirable characteristic or property, namely P2X7 receptor antagonist and TNF α inhibitor. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT).

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to claims 2-7 and 9-11.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2004/000817

EP	1310493	A1	14/05/2003	BR	0204588 A	16/09/2003
				CA	2411544 A	12/05/2003
				JP	2003183263 A	03/07/2003
				US	20030144293 A	31/07/2003
				WO	03042190 A	22/05/2003

WO	03042191	A1	22/05/2003	CA	2466724 A	22/05/2003
				US	20030186981 A	02/10/2003

WO	03041707	A1	22/05/2003	CA	2464863 A	22/05/2003
				SE	0103836 D	00/00/0000

WO	0144170	A1	21/06/2001	AT	261933 T	15/04/2004
				AU	2244401 A	25/06/2001
				BR	0016395 A	27/08/2002
				CA	2393352 A	21/06/2001
				CN	1434794 T	06/08/2003
				CZ	20022093 A	15/01/2003
				DE	60009147 D	00/00/0000
				DK	1242364 T	21/06/2004
				EE	200200330 A	15/10/2003
				EP	1242364 A,B	25/09/2002
				SE	1242364 T3	
				EP	1352895 A	15/10/2003
				EP	1352896 A	15/10/2003
				EP	1352897 A	15/10/2003
				GB	0015744 D	00/00/0000
				HU	0300616 A	28/07/2003
				IL	150124 D	00/00/0000
				JP	2003517035 T	20/05/2003
				NO	20022856 A	16/08/2002
				NZ	519378 A	27/02/2004
				PL	355913 A	31/05/2004
				SK	8412002 A	04/02/2003
				US	20030013704 A	16/01/2003
				GB	0017942 D	00/00/0000
				SE	9904651 D	00/00/0000
				ZA	200204125 A	25/08/2003

INTERNATIONAL SEARCH REPORT

Internauonal application No.

PCT/SE 2004/000817

WO	0142194	A1	14/06/2001	AT	263748	T	15/04/2004
				AU	2036301	A	18/06/2001
				BR	0016227	A	01/10/2002
				CA	2394236	A	14/06/2001
				CN	1407968	T	02/04/2003
				CZ	20021982	A	15/01/2003
				EE	200200295	A	15/08/2003
				EP	1240132	A,B	18/09/2002
				SE	1240132	T3	
				HU	0300618	A	28/07/2003
				IL	149762	D	00/00/0000
				JP	2003516382	T	13/05/2003
				NO	20022727	A	29/07/2002
				NZ	518985	A	27/02/2004
				SE	9904505	D	00/00/0000
				SK	7622002	A	09/01/2003
				US	6720452	B	13/04/2004
				US	20020193414	A	19/12/2002
				ZA	200203834	A	14/08/2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/07/2004

International application No.

PCT/SE 2004/000817

WO	0061569	A1	19/10/2000	AU	774526	B	01/07/2004
				AU	3994700	A	14/11/2000
				AU	5547000	A	02/01/2001
				BR	0009651	A	08/01/2002
				CA	2368829	A	19/10/2000
				CN	1353702	T	12/06/2002
				CZ	20013608	A	15/05/2002
				EE	200100525	A	16/12/2002
				EP	1171432	A	16/01/2002
				GB	0002330	D	00/00/0000
				HU	0202214	A	28/10/2002
				IL	145505	D	00/00/0000
				JP	2002541249	T	03/12/2002
				NO	20014894	A	10/12/2001
				NZ	514477	A	29/04/2003
				PL	350907	A	10/02/2003
				SK	13422001	A	09/05/2002
				TR	200102911	T	00/00/0000
				US	6492355	B	10/12/2002
				AP	200102041	D	00/00/0000
				AT	250036	T	15/10/2003
				AU	751103	B	08/08/2002
				AU	4950499	A	07/02/2000
				BR	9912109	A	02/05/2001
				CA	2336968	A	27/01/2000
				DE	69911415	D,T	08/07/2004
				DK	1095021	T	24/11/2003
				EE	200100010	A	17/06/2002
				EP	1095021	A,B	02/05/2001
				SE	1095021	T3	
				HK	1035715	A	00/00/0000
				HR	20010039	A	31/12/2001
				HU	0103224	A	28/01/2002
				IL	140346	D	00/00/0000
				JP	2002520395	T	09/07/2002
				NO	20010211	A	15/03/2001
				NZ	508923	A	27/09/2002
				PL	345388	A	17/12/2001
				SE	9901270	D	00/00/0000
				ZA	200108265	A	08/01/2003